Guidance for Industry

Inhalational Anthrax (Post-Exposure) — Developing Antimicrobial Drugs

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Brad Leissa 301-827-2350.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2002
Clinical Antimicrobial

02D- 00 02   G-DL 1

Guidance for Industry

Inhalational Anthrax (Post-Exposure) — Developing Antimicrobial Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2002
Clinical Antimicrobial

TABLE OF CONTENTS

26
27
28
29
30
31

Guidance for Industry[1]

Inhalational Anthrax (Post-Exposure)—
Developing Antimicrobial Drugs

36
37
38
39   ## I.   INTRODUCTION
40
41   In response to the recent bioterrorism event involving exposure to *Bacillus anthracis*, FDA has
42   been approached by a number of firms seeking guidance on how to develop additional therapies
43   and ultimately to receive FDA-approved labeling for anthrax. This guidance focuses on the
44   development of antimicrobial drugs for administration to persons who have inhaled aerosolized
45   *Bacillus anthracis*, but who do not yet have the established disease. The treatment goal would be
46   to prevent the development of disease in such persons following exposure to *B. anthracis* spores.
47
48   This guidance is *not* intended to provide recommendations on how to treat the established
49   disease, whether inhalational anthrax, gastrointestinal anthrax, or cutaneous anthrax. This
50   guidance also does *not* address the use of other means of managing patient exposure, public
51   health agency roles, drug stockpiles, or deployment of agents following an exposure to *B.*
52   *anthracis.*
53
54   This is one in a series of guidance documents intended to assist the pharmaceutical industry in
55   the development of antimicrobial drug products for the treatment or prevention of infections.
56   The information presented here should help applicants plan, design, conduct, and appropriately
57   monitor the studies, including clinical studies, to collect relevant data for analysis, and perform
58   appropriate types and numbers of analyses of study data. Before a drug can receive a labeled
59   indication for inhalational anthrax (post-exposure), the sponsor should have extensive
60   postmarketing experience with their drug, including, ideally, prolonged drug dosing safety
61   information. For an intended use where large populations may be indicated to receive prolonged
62   antimicrobial drug dosing, extensive post-marketing safety experience is needed to formulate a
63   risk-benefit analysis between the potential benefit of effective drug therapy and the risks of
64   inhalational anthrax spore exposure and prolonged drug dosing.

65
66   Applications submitted to the Agency on studies conducted as recommended in this guidance
67   should yield the information necessary for the Agency to determine whether the antimicrobial
68   under study is safe and effective for use in persons exposed to aerosolized *B. anthracis* who do
69   not yet have established disease. For general information on antimicrobial drug development,
70   the reader is referred to the guidance *Developing Antimicrobial Drugs — General*
71   *Considerations for Clinical Trials (General Considerations)*.
72
73   **II.   BACKGROUND**
74
75   In the fall of 2001, *B. anthracis*, the bacterium that causes anthrax, was used as a bioterrorism
76   agent and sent through the U.S. mail, resulting in cases of cutaneous and inhalational anthrax in
77   New York, New Jersey, the District of Columbia, Maryland, Virginia, Florida, and Connecticut.
78   Until this time, anthrax was exceedingly rare in the United States. Approximately 220 cases of
79   cutaneous anthrax (CDC 2000) and 18 cases of inhalational anthrax (Brachman 1980) were
80   reported in the United States in the 20th century. Before 2001, the last reported case of
81   inhalational anthrax occurred in 1976 (Suffin et al., 1978). More recent recognized outbreaks
82   were reported in other parts of the world, including an outbreak in 1979, when in Sverdlovsk
83   (currently Ekaterinburg), Russia, 66 people died of inhalational anthrax after *B. anthracis* spores
84   were accidentally released from a Soviet military laboratory (Meselson et al., 1979). Data
85   available from 41 autopsies have contributed to our present knowledge concerning disease
86   pathogenesis.
87
88   A window of opportunity for preventive therapy exists between the time of inhalation of
89   aerosolized spores of *B. anthracis* and development of signs and symptoms of disease. Evidence
90   from animal models and recent human experience has demonstrated use of certain antimicrobial
91   agents ***after*** the inhalational exposure to *B. anthracis* spores, but ***before*** the development of
92   disease symptoms can be effective in preventing the disease and reducing mortality. As a result,
93   the Agency is encouraging the development of antimicrobial agents to be used in the event of
94   inhalational exposure to *B. anthracis*. This guidance provides recommendations on how to
95   develop such agents and gives examples of agents that have met approval criteria.
96
97   **A.   Disease Description**
98
99   Anthrax is a bacterial infection caused by the gram-positive bacillus, *B. anthracis*.
100   A disease of antiquity, anthrax was responsible for major epidemics and mortality. The
101   incidence of the disease declined rapidly after the etiologic role of *B. anthracis* was
102   recognized and scientists such as Robert Koch and Louis Pasteur worked to introduce
103   control measures and animal vaccination.
104

105	Three types of infections are recognized in humans: cutaneous, gastrointestinal, and
106	inhalational disease. Cutaneous anthrax occurs when spores gain access through a cut or
107	abrasion in the skin. The organisms germinate and produce toxins that result in a local
108	reaction with swelling and eschar formation. The disease may progress to bacteremia,
109	and mortality is reported in up to 20 percent of untreated cutaneous cases. Cutaneous
110	anthrax can be recognized clinically, and morbidity and mortality are low with
111	appropriate antimicrobial therapy. Gastrointestinal disease is usually associated with the
112	ingestion of anthrax-contaminated meat. Gastrointestinal disease can be prevented
113	through the effective inspection of livestock and meat products entering the marketplace.
114	Inhalational anthrax follows aerosolized exposure to the spores of *B. anthracis* with
115	subsequent germination of the spores, toxin production, and invasion of the tissues and
116	blood stream by the organism. After a usual incubation period of 2 to 6 days, exposed
117	individuals develop symptomatic disease with very high mortality.
118	
119	Inhalational anthrax was encountered as recently as the 19th century in industrial settings
120	when large numbers of spores were aerosolized in certain factories (e.g., woolsorter's
121	disease or ragpicker's disease) (Plotkin et al., 1960). Mortality for established disease,
122	even after treatment, was 80 to 100 percent in the 20th century. These rates may change
123	as established disease is treated in the 21st century.
124	

B.   Histology

126	
127	Extensive edema, necrosis, and hemorrhage into affected tissues, including the
128	mediastinal and hilar lymph nodes, the gastrointestinal tract, and the meninges
129	characterize histopathologic changes in human anthrax. Notably, given the respiratory
130	route of entry of the spores and deposition within the alveoli, there are only rare reports
131	of pulmonary bacterial pneumonia, such as consolidation, and inflammation within the
132	pulmonary parenchyma. However, pleural effusions are common.
133	

C.   Microbiology

| 135 | |

1.   In vitro susceptibility testing

137	
138	Currently, there are no standardized methods (e.g., disk diffusion, broth dilution, or agar
139	dilution) for the susceptibility testing of *B. anthracis*. During the bioterrorism events of
140	2001, the Centers for Disease Control and Prevention (CDC) evaluated the minimal
141	inhibitory concentrations (MICs) of several antimicrobials against the causative strains of
142	*B. anthracis* using the current National Committee for Clinical Laboratory Standards
143	(NCCLS) broth dilution method (NCCLS 2000). The suitability of the current NCCLS
144	broth dilution testing method for susceptibility testing of drugs against *B. anthracis* is
145	under evaluation by the FDA, CDC, and NCCLS. Interpretive criteria by which an
146	isolate of *B. anthracis* may be defined as susceptible or resistant to a particular
147	antimicrobial have not been determined. The Agency recommends that applicants
148	contact the NCCLS for the latest information on susceptibility testing of *B. anthracis*.[2]

---

[2] NCCLS can be contacted at www.NCCLS.org.

149
150 ## 2. Mechanisms of resistance
151
152 The isolates of *B. anthracis* used during the Fall 2001 bioterrorism episodes have not
153 demonstrated high minimum inhibitory concentrations (MICs) to any of the
154 antimicrobials tested. However, the existing literature on the susceptibility of *B.*
155 *anthracis* suggests that some strains may be penicillin resistant (Lightfoot et al., 1990).
156 In addition, the potential for multi-drug resistant strains of *B. anthracis* exists (Inglesley
157 et al., 1999). Russian scientists claim to have produced a vaccine strain of *B. anthracis*
158 that is resistant to penicillin and doxycycline (Stepanov et al., 1996). The potential for
159 drug resistance supports the study of several classes of antimicrobials to prevent the
160 development of inhalational anthrax.
161
162 The clinical relevance and importance of resistance mechanisms in strains of *B. anthracis*
163 remains unclear. For example, certain strains of *B. anthracis* may produce beta-
164 lactamases but administration of penicillin in animal models appears to prevent disease
165 with these same strains. It is clear that microbiologic testing of isolates should be
166 performed before and after drug exposure as part of the evaluation of products for
167 prevention of inhalational anthrax. However, although the MICs for the extended-
168 spectrum cephalopsporins are not high, the efficacy of these drugs for the treatment of *B.*
169 *anthracis* infection is unclear (Inglesby, et al., 1999).
170
171
172 ## III. THE MONKEY MODEL — APPLICABILITY TO THE HUMAN DISEASE
173
174 Because clinical studies of inhalational anthrax cannot be performed in humans (one cannot
175 ethically intentionally expose patients to *B. anthracis* spores and randomize to active or placebo
176 arms), the Agency has to rely on other evidence of efficacy for this indication. After much
177 discussion and consideration, including input from the Anti-Infective Advisory Committee, the
178 Agency believes that the use of the rhesus (macaque) monkey disease and treatment model for
179 inhalational anthrax (post-exposure) provides convincing evidence of efficacy for regulatory
180 purposes. The parallels, summarized here, between the rhesus monkey disease and treatment
181 model and the human circumstance were noted by the Committee:
182
183 Exposure: The spores gained access to the respiratory tract via an aerosol as would be
184 expected in human inhalational anthrax.
185
186 Antimicrobial use: The antimicrobials currently approved or found effective
187 (ciprofloxacin, doxycycline, penicillin G procaine) were administered by the same route
188 (oral or IM) and in the same q12h regimen in monkeys as was ultimately the
189 recommended route and frequency in humans.
190
191 Antimicrobial Pharmacokinetics: For the drugs that have been granted regulatory
192 approval for this indication, the peak and trough plasma concentrations measured in the
193 rhesus model were similar to peak and trough plasma concentrations measured in
194 humans.
195

196	Time course: The time course of the disease among untreated animals — short
197	incubation, rapid down hill course, mortality — is similar to that among people who died
198	of inhalational anthrax in Sverdlovsk in 1979 and in the United States in the fall of 2001.
199	
200	Histopathology: The autopsy findings of inhalational anthrax reported from the
201	Sverdlovsk experience and reviewed by Dr. Walker at the July 28, 2000, Anti-Infective
202	Advisory Committee meeting are strikingly similar to the necropsy findings reported by
203	Dr. Friedlander in the monkeys that died of inhalational anthrax. Other published
204	literature support these comparative histopathological findings. (Fritz et al, 1995; Gleiser
205	et al, 1967.)
206	
207	Antimicrobial Activity in Monkey Model: For the drugs currently approved for this
208	indication, the efficacy of the antimicrobial product (ciprofloxacin, doxycycline,
209	penicillin G procaine) compared to saline placebo showed a statistically significant
210	difference in favor of antimicrobial administration, whether one looked at the intent to
211	treat analysis (all animals studied) or the per protocol analysis (anthrax deaths).
212	
213	A study indicating that another species of monkey was interchangeable with rhesus monkeys
214	would be considered by the Agency. The data from a monkey study could be submitted as long
215	as the model is used in conjunction with data from other sources, including:
216	
217	• in vitro sensitivity data on *B. anthracis*
218	• pharmacokinetic data in animals and in humans
219	• information on drug efficacy in treating other infections
220	• evidence of safety up to and exceeding 60 days
221	
222	This information, as well as convincing evidence from the rhesus monkey model, should be
223	submitted in the application for approval.
224	
225	

226 **IV.   DRUGS EFFECTIVE IN MANAGING PATIENTS**

227	
228	On August 30, 2000, the Agency approved ciprofloxacin hydrochloride tablets, ciprofloxacin
229	intravenous (IV) solution, ciprofloxacin IV in 5 percent dextrose, ciprofloxacin IV in 0.9 percent
230	saline, and ciprofloxacin oral suspension for use in the management of patients who have been
231	exposed to aerosolized spores of *B. anthracis* as a 60-day regimen. The new drug applications
232	(NDAs) submitted by the sponsor for these products included in vitro activity information,
233	pharmacokinetic data in humans and monkeys, long-term safety data on ciprofloxacin, and the
234	results of an efficacy study in nonhuman primates. This information was brought before the
235	Anti-Infective Advisory Committee with a recommendation for approval of the indication and a
236	dosing duration of 60 days.[3]
237	
238	On November 2, 2001, in a public health response to the use of anthrax spores as a bioterrorism
239	agent, the Agency published a notice in the *Federal Register* (66 FR 55679) that clarified the

---

[3] See transcript of meeting at http://www.fda.gov/cder/drug/infopage/cipro/default.htm.

240 dosing recommendations for doxycycline products and penicillin G procaine in the management
241 of patients with inhalational anthrax who had been exposed to the spores of *B. anthracis*, but
242 who did not manifest clinical disease.[4] Drug products containing doxycycline, doxycycline
243 calcium, doxycycline hyclate, and penicillin G procaine had already been approved with
244 indications for anthrax. The *Federal Register* notice stated that the Agency "determined that the
245 language in the labeling of drug products containing doxycycline, doxycycline calcium,
246 doxycycline hyclate, and penicillin G procaine is intended to, and does, cover all forms of
247 anthrax, including inhalational anthrax (post-exposure): to reduce the incidence or progression
248 of disease following exposure to aerosolized *B. anthracis.*" The *Federal Register* notice further
249 requested that applicants for these products submit labeling supplements to update their package
250 inserts with this information.
251
252 It is relevant to the above information on ciprofloxacin, doxycycline, and penicillin G procaine
253 that the rhesus monkey study supporting the approval of ciprofloxacin also included separate
254 doxycycline and penicillin G procaine treatment arms. Each of these arms showed a survival
255 advantage over placebo (Friedlander et al., 1993). No other antimicrobial drugs were tested in
256 this study.[5]
257
258 The *Federal Register* notice also explained that other drug products are currently approved with
259 indications for anthrax or infections caused by *B. anthracis* (i.e., minocycline, tetracycline,
260 oxytetracycline, demeclocycline, and penicillin G potassium), that data on these other drugs were
261 undergoing review, and that additional data might be needed to make an explicit labeling
262 recommendation for their use in inhalational anthrax (post-exposure). This notice served to guide
263 the regulatory decisions regarding ciprofloxacin, doxycycline, and penicillin G procaine.
264
265
266 ## V.   INHALATIONAL ANTHRAX (POST-EXPOSURE)
267
268 The safety and effectiveness of an antimicrobial to either prevent or treat disease following
269 aerosolized exposure to *B. anthracis* cannot be tested in humans because the naturally occurring
270 disease is rare, and it is unethical to expose humans to the bacteria intentionally. As a result, an
271 application requesting approval of a drug for the indication INHALATIONAL ANTHRAX
272 (POST-EXPOSURE) should contain the elements discussed in detail in this section. Studies
273 planned and conducted as recommended in this guidance should yield the information necessary
274 for the Agency to determine whether the antimicrobial under study is safe and effective in the
275 management of this condition.
276
277 This guidance serves as our best advice under the current scenario where approved therapies are
278 available and the country is not in a state of massive-scale exposure to *B. anthracis*. In the event
279 of a large-scale exposure or absence of other approved therapies (e.g., because supplies are
280 exhausted or otherwise unavailable), the Agency would provide emergency guidance on an
281 alternative approach.

---

[4] See information at http://www.fda.gov/cder/drug/infopage/penG_doxy/default.htm or www.gpo.gov.

[5] See July 28, 2000, Advisory Committee transcript http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective.

282
283 Applications that can meet some of the elements listed below can request fast track designation
284 while completing the development of data on the other elements.[6]
285
286 ### A.   The Indication: Regulatory Synonyms
287
288 The Agency has determined that the indication should be designated INHALATIONAL
289 ANTHRAX (POST-EXPOSURE) with further clarification that administration of an
290 antimicrobial is intended "to reduce the incidence or progression of disease following
291 exposure to aerosolized *B. anthracis*."
292
293 Specifically, this means that drug administration should start ***after*** a known or suspected
294 exposure to the aerosolized spores of *B. anthracis*, but ***before*** clinical symptoms of the
295 disease develop. Some refer to this intended indication *as post-exposure prophylaxis*
296 even though the intended administration of drug is after the exposure to *B. anthracis*.
297
298 The purpose of specifying this indication is to distinguish it from (1) the treatment of
299 symptomatic, established inhalational anthrax infection, which is accompanied by a
300 substantial morbidity and (2) prophylaxis of the disease, namely, administering the drug
301 before exposure to *B. anthracis*.
302
303 ### B.   Chemistry
304
305 There are no expected chemistry issues because it is anticipated that the drug product
306 already will have been approved in the United States.
307
308 ### C.   Preclinical Toxicology Data
309
310 It is anticipated that the drug product under development already will have been approved
311 for marketing and that data are available in the approved NDA on animal toxicity in at
312 least two species (e.g., rat, mouse, dog, monkey) for durations up to 6 months. If clinical
313 data and experience demonstrate that a 60-day course of therapy would be reasonably
314 safe to administer to humans, long-term animal toxicology data would not be necessary.
315 (The drugs currently approved have been on the market from 10 to 50 years and already
316 exceed 100 million treatment courses in the United States with additional experience
317 worldwide.) Carcinogenicity studies may provide useful information, but are not
318 necessary for the same reason.
319
320 ### D.   In Vitro Microbiology Data
321
322 When ciprofloxacin was approved and the findings of efficacy published for doxycycline
323 and penicillin G procaine, the available information on in vitro sensitivity of *B. anthracis*
324 to these antimicrobials was extensive. The Agency had information on more than 90
325 isolates. When submitting a supplemental application for this indication, it would be

---

[6] See guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review* (September 1998).

326 reasonable to submit a smaller number of isolates, particularly if there is evidence that all
327 isolates have uniformly low MICs to the drug of interest.
328
329 *Note*: The term *low MICs* is used because the FDA and NCCLS have not established
330 susceptibility breakpoints for this organism. Therefore, it would be inappropriate to state
331 that the isolates are uniformly susceptible. The goal of the in vitro testing is to
332 demonstrate that low concentrations of a drug (below those that could be achieved in
333 dosing in humans) reliably inhibit growth of *B. anthracis*. Depending on the consistency
334 and uniformity of MICs determined when testing a particular drug, it is possible that 30
335 to 50 isolates would be adequate. With multiple-fold variability in the MIC results, data
336 on a larger number of isolates should be submitted.
337
338 In summary, we recommend the following:
339
340 • Several strains (including Vollum, Ames, Sterne, and others) and multiple isolates
341   (from 30 to 90, as discussed above) should be tested.

342 • Testing should be done in at least two to three laboratories, and at least some of the
343   same isolates should be tested by these laboratories to demonstrate reproducibility of
344   MIC results.

345 • During testing, ciprofloxacin, doxycycline and/or penicillin G should be used as
346   control drugs.

347 • All susceptibility testing should include a wide enough range of concentrations so that
348   all MICs have an exact quantitative value instead of < *some value* or > *some value*.

349 • The details of the testing should be documented (e.g., a protocol should be provided).

350 • If antimicrobial resistance is detected, the mechanism should be characterized.

351 • Efforts should be made to measure the potential for development of resistance in
352   vitro. This testing should include studies to determine the frequency of spontaneous
353   mutation and the emergence of multistep resistance in the presence of the compound.
354   Another drug such as ciprofloxacin, doxycycline, or penicillin should be included as a
355   comparator. Once such information is available, attempts should be made to correlate
356   the mutation frequency with clinical outcome.

357 • Studies to measure reciprocal cross-resistance should also be considered using other
358   drugs such as ciprofloxacin, doxycycline, and penicillin G (the three drugs now found
359   to be effective for post-exposure inhalational anthrax).
360
361 **E.   Rhesus Monkey and Other Animal Models of Efficacy**
362
363 The Agency believes that until a better approach can be identified to approve drugs for
364 use in persons exposed to aerosolized *B. anthracis*, the rhesus monkey model
365 (Friedlander 1993) should be used for testing additional drugs. A study or data indicating
366 that another species of monkey is interchangeable with rhesus monkeys would be
367 considered by the Agency. The value of using this model is the similarity of (1) the
368 disease, (2) the response to therapy, and (3) systemic drug exposure in the primate model
369 when compared to humans. There also is value in replicating the efficacy results shown

370 in the original study. Study results should be available at the time the supplement is
371 submitted, not as part of a phase 4 commitment.
372
373 In summary, the following general recommendations should be followed:
374
375 • The drug should be tested in a nonhuman primate model.

376 • A vehicle control group should be included. This would serve as a negative control to
377 determine the progression of disease in the absence of treatment.

378 • Consider using penicillin, doxycycline, and/or ciprofloxacin as a positive control.
379 This approach can serve as an active control and provide for replication of results
380 from the initial study conducted by Friedlander et al., (1993).

381 • At least 10 animals per arm should be studied.

382 • Treatment should continue for 30 days.

383 • There should be a 70-day follow-up observation period after treatment is completed,
384 for a total study duration of 100 days.

385 • Specify dose and dosage regimen. Animal dosages should be determined based on
386 the anticipated human dosage regimen. The animal dose should give systemic
387 exposures comparable to the anticipated human exposure, and the drug regimen (e.g.,
388 QD, BID) should be the same as anticipated in humans. In addition, periodic
389 measurement of peak and trough levels should be done in animals during the study to
390 confirm the level of drug exposure.

391 • The route of drug administration in animals should be applicable to human use.

392 • Blood samples for pharmacokinetic (PK) analysis should be collected from each
393 drug-treated monkey. At a minimum, blood samples should be collected to determine
394 plasma drug concentrations at the approximate time of maximum concentration (peak
395 or Cmax) and at the end of the dosing interval (trough or Cmin), after first dose
396 administration and for several successive days after steady state has been attained (at
397 least 5 Cmax and 5 Cmin determinations).

398 • End points should include survival, bacteremia at different time intervals during or
399 after treatment, and microbial burden in infected organs and/or tissues (e.g., blood,
400 spleen, liver) collected at the time of necropsy.

401 • Bacteria cultured from animals that develop infection either on treatment or in the 60-
402 day followup period should be tested for in vitro sensitivity to determine MICs. The
403 MICs after treatment should be compared to the baseline values.

404 • Histopathology data on animals that died during the study should be recorded.

405 Applicants should also consider developing models using small animals (e.g., guinea
406 pigs), which may be more readily available and which could be used for further study of
407 drugs, drug dosing, drug regimens, and drug duration, as well as exploring drug regimens
408 and drug combinations for treatment of established disease. Although not required, the
409 development of such models would benefit public health by advancing the science and
410 knowledge in the area of animal models for the study of disease caused by *B. anthracis*.

411
412   In addition, applicants may wish to explore the possibility of studies in other nonhuman
413   primates such as cynomologous or African green monkeys.
414
415   **F.   Clinical Pharmacology**
416
417   It is important to obtain complete pharmacokinetic data on the drug in human volunteers
418   or patients and pharmacokinetic data in the rhesus monkey in the efficacy study of
419   inhalational anthrax (post-exposure). The purpose of obtaining these data is to
420   demonstrate that the desired systemic exposure achieved in humans after the anticipated
421   dosage regimen can actually be achieved and is effective in the animal model in
422   preventing inhalational anthrax infection and consequent mortality. Alternatively, it is
423   important to demonstrate that the systemic exposure to the antimicrobial achieved in the
424   rhesus monkey and found effective in preventing infection and death is an exposure that
425   is achievable in humans with an approved and/or otherwise safe-to-use dosage.
426
427   In summary, we recommend the following:
428
429   •   The doses to be tested in animals and in humans should be determined. A
430   pharmacokinetic/pharmacodynamic (PK/PD) approach may be helpful in the
431   determination of an appropriate dosage regimen. For example, use of PK/PD
432   parameters such as AUC/MIC and/or Cmax/MIC may be useful for antimicrobial
433   drugs with concentration-dependent mechanisms of bacterial killing, while the
434   time above the MIC (T_{MIC}) may be useful for antimicrobial drugs with time-
435   dependent mechanisms of bacterial killing.

436   •   The route of administration should be designated and should be the same in both
437   monkeys and humans.

438   •   Each of at least 10 monkeys should have both peak and trough plasma
439   concentrations determined at least 5 times during the study.

440   •   Because it is anticipated that the drug to be tested already will be on the market,
441   adequate pharmacokinetic data should already be available in package labeling or
442   in the literature. If such information is not available, the sponsor should provide
443   pharmacokinetic data after single-dose and repeat-dose administration from an
444   adequate number of male and female subjects for the purpose of providing
445   descriptive statistics and to show comparable systemic drug exposure to that in
446   the animal models used to study the drug for inhalational anthrax (post-exposure).

447   •   Pharmacokinetic data for special populations, including pediatric patients, elderly
448   subjects (≥ 65 years), and subjects with renal and hepatic impairment should be
449   *   provided.
450
451   •   Available pharmacokinetic data in pregnant women should be submitted.
452
453   •   Available data for drug excretion into human breast milk should be submitted.
454

455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500

- Available pharmacokinetic data in the animals chosen for study of the drug for inhalational anthrax (post-exposure) and comparison of the pharmacokinetic and/or systemic exposure between the animals and humans should be submitted.

- Full characterization of the metabolic profile (in vitro and in vivo) in humans and in the animals chosen to study the drug for inhalational anthrax (post-exposure) should be provided.

- Information regarding the potential for pharmacokinetic drug interactions in humans should be submitted.

- Information comparing the plasma protein binding of the drug in the chosen animals and in humans should be submitted.

G.   Efficacy in Humans for Other Indications

It is expected that in the event of a large-scale exposure to anthrax, large numbers of people would be administered antimicrobials to prevent symptomatic infection by *B. anthracis*. As a result, the Agency recommends that drugs to be developed for this use already be on the market and already show their effectiveness in the treatment of a range of infectious diseases, which may include, but need not be limited to, respiratory, mediastinal, intra-abdominal, bone, or meningeal infections.

In summary, we recommend the following:

- The drug to be evaluated should already be an approved *and marketed* drug.

- The drug should be safe and effective in the treatment of a range of infectious diseases due to a variety of pathogens.

H.   Evidence of Long-Term Safety in Humans

Because the anticipated duration of therapy for patients exposed to inhaled anthrax spores is at least 60 days, there should be sufficient data on prolonged use of the drug in large numbers of patients. The drug should have shown few and self-limited, or reversible, adverse events. For example, ciprofloxacin was initially approved in 1987. By the time of approval for inhalational anthrax (post-exposure) in 2000, the drug had been prescribed to at least 100 million patients for the treatment of other infections. Doxycycline and penicillin G procaine both have been on the worldwide market for more than 30 and 50 years, respectively.

The sponsor should provide any data on adverse events that may be unique or more common with longer duration of dosing compared to shorter courses of therapy. In addition to long-term safety data, sponsors should provide marketing information on all applicable formulations, including solid oral dosage forms, pediatric oral dosage forms, and parenteral dosing forms.

501	Finally, the Agency is interested in reviewing all available data on the safety of the drug
502	in relevant subpopulations, including geriatric patients, adults, the pediatric population,
503	and pregnant women. Information on patients with kidney or renal impairment, as
504	appropriate, also should be submitted.
505	
506	**I. Statistics**
507	
508	In the animal model to support approval, the antimicrobial drug must demonstrate
509	efficacy, that is, it must be shown to be statistically superior to placebo (21 CFR 314.510
510	and 314.126).
511	
512	**J. Regulatory Issues**
513	
514	Unless it already carries an anthrax indication (e.g., tetracycline class agents, aqueous
515	penicillin G), the drug would be approved under § 314.500, Subpart H, accelerated
516	approval. This approval would be based on the surrogate endpoint of the relationship
517	between serum concentrations in humans and animals, in the context of the animal model
518	of efficacy, as was the case for ciprofloxacin.
519	
520	**K. Labeling**
521	
522	Once the supplement has been approved, labeling should:
523	
524	• List the organism in the in vitro microbiology subsection
525	*Note*: The Agency does not believe including this particular organism in the in vitro
526	section of the labeling in the absence of data supporting approval of the indication is
527	appropriate.
528	• List the indication (e.g., inhalational anthrax (post exposure))
529	• Provide the appropriate dosing regimen
530	• Provide the regulatory information forming the basis of approval
531	• Provide a summary of the data that served as the basis of approval
532	
533	**L. Postapproval Commitments and/or Requirements**
534	
535	Because it is anticipated that these drugs would be approved for inhalational anthrax
536	(post-exposure) under Subpart H regulations (§ 314.500), the approval letter would
537	request that confirmatory clinical data be provided in the event of an accidental or
538	intentional exposure to aerosolized *B. anthracis* (§ 314.510). Applicants should include
539	as part of their application a plan or approach to obtaining such confirmatory data in the
540	event such studies become ethical and feasible as a result of such an exposure. Among
541	other information, relevant data would include patient identifying information, a listing of
542	the drugs that were used, and data on compliance, adverse reactions, and outcomes.
543	Sponsors may wish to consult with the division about the contents of their postmarketing
544	study plan before submission to the Agency. In addition, the company would agree to
545	cooperate with relevant U.S.-based public health agencies in the collection and evaluation

546 of data on the use of the drug product in a large U.S. population exposed to *B. anthracis*,
547 should such an exposure occur.
548
549 Under Subpart H regulations, the company also would have to have any advertising or
550 promotional material for this indication cleared by the Agency before use (§ 314.550).
551
552
553 **VI. SUMMARY**
554
555 In summary, we recommend that the applicant provide information on the following:
556
557 • In vitro antimicrobial sensitivity data on an adequate number of isolates, reflecting the
558 spectrum of available isolates and taking into consideration the possibility of engineered
559 resistant strains
560 • Clinical pharmacology data on the proposed dosing regimen of the product
561 • Safety data, including preclinical and clinical dose and duration data that support the use
562 of this product for long durations up to at least 60 days
563 • Evidence of extensive use of the product including use in geriatric patients, adults, the
564 pediatric population, pregnant women, and any other special populations
565 • Efficacy data in humans. Priority will be given to drugs that have been approved for a
566 variety of indications and have a fairly substantial marketing history.
567 • Efficacy, pharmacokinetic and histopathology data from nonhuman primate models of
568 inhalational anthrax. Efficacy data should be submitted based on a study of the
569 antimicrobial in a nonhuman primate model of inhalational anthrax that replicates the
570 Friedlander study. Other animal models may be used once the Friedlander study has
571 been replicated successfully with studies of other antimicrobials for inhalational anthrax
572 (post-exposure) and those animal models have been validated. Other animal models
573 could include nonhuman primates other than rhesus monkeys and smaller animals. The
574 ultimate goal of such studies is to find a small animal model with more readily available
575 animals to replace the rhesus monkey model so that more specific and detailed testing of
576 dosing, duration, and combinations can be done.
577

REFERENCES

Centers for Disease Control and Prevention (CDC), 2000, "Human Anthrax Associated with an Epizootic Among Livestock – North Dakota," *MMWR.*, 50(32):677-680.

Brachman, P. S., 1980, "Inhalational Anthrax," *Ann NY Acad Sci.*, 353:83-93.

Friedlander, A. M., S. L. Welkos, M. L. M. Pitt, et al., 1993, "Post-Exposure Prophylaxis Against Experimental Inhalation Anthrax," *J Infect Dis.*, 167:1239-1242.

Fritz, D.L., Jaax, N.K., Lawrence, W.B., et al. 1995, "Pathology of Experimental Inhalation Anthrax in the Rhesus Monkey," *Lab Invest.*, 73:691-702

Gleiser, C.A., 1967, "Pathology of Anthrax Infection in Animal Hosts," *Fed Proc.*, 26:1518-1521.

Henderson, D. W., S. Peacock, and F. C. Belton, 1956, "Observations on the Prophylaxis of Experimental Pulmonary Anthrax in the Monkey," *J. Hyg.*, 54:28-36.

Inglesby, T. V., D. A Henderson, J. G. Bartlett, et al., 1999, "Anthrax As a Biological Weapon," *JAMA*, 281(18):1735-1745.

Lightfoot, N.F., R.J.D. Scott, and P.C.B. Turnbull, 1990, "Antimicrobial Susceptibility of *Bacillus anthracis*," *Salisbury Med Bull.*, 68 special supplement:95-98.

Meselson, M., J. Guillemin, M. Hugh-Jones, et al., 1994, "The Sverdlovsk Anthrax Outbreak of 1979," *Science,* 266:1202-1208.

National Committee for Clinical Laboratory Standards, 2000, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Fifth Edition*, M7-A5, 20: No. 2.

Plotkin, S. A., P. S. Brachman, M. Utell, et al., 1960, "An Epidemic of Inhalational Anthrax, the First in the Twentieth Century," *Am J Med*, 29:992-1001.

Stepanov, A. V., L. I. Marinin, A. P. Pomerantsev, et al., 1996, "Development of Novel Vaccines Against Anthrax in Man," *J Biotechnol.*, 44:155-160.

Suffin, S. C., W. H. Carnes, A. F. Kaufmann, et al., 1978, "Inhalational Anthrax in a Home Craftsman," *Human Pathology,* 9(5):594-597.